

# RF-Interrogatable Hydrogel-Actuated Biosensor

*Z.A. Hoel, A.W. Wang, C.B. Darrow, A.P. Lee, C.F.  
McConaghy, P. Krulevitch, A. Gilman, J.H. Satcher, S.M.  
Lane*

This article was submitted to  
11<sup>th</sup> International Conference on Mechanics in Medicine and  
Biology, Maui, HI, April 2-5, 2000

**January 10, 2000**

**U.S. Department of Energy**

Lawrence  
Livermore  
National  
Laboratory

## DISCLAIMER

This document was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor the University of California nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or the University of California. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or the University of California, and shall not be used for advertising or product endorsement purposes.

This is a preprint of a paper intended for publication in a journal or proceedings. Since changes may be made before publication, this preprint is made available with the understanding that it will not be cited or reproduced without the permission of the author.

This report has been reproduced  
directly from the best available copy.

Available to DOE and DOE contractors from the  
Office of Scientific and Technical Information  
P.O. Box 62, Oak Ridge, TN 37831  
Prices available from (423) 576-8401  
<http://apollo.osti.gov/bridge/>

Available to the public from the  
National Technical Information Service  
U.S. Department of Commerce  
5285 Port Royal Rd.,  
Springfield, VA 22161  
<http://www.ntis.gov/>

OR

Lawrence Livermore National Laboratory  
Technical Information Department's Digital Library  
<http://www.llnl.gov/tid/Library.html>

## RF-INTERROGATABLE HYDROGEL-ACTUATED BIOSENSOR

Zoe A. Hoel\*, Amy W. Wang\*, Christopher B. Darrow, Abraham P. Lee, Charles F. McConaghy, Peter Krulevitch, Aleksandr Gilman, Joe H. Satcher, Stephen M. Lane

Center for Microtechnology, Lawrence Livermore National Laboratory

7000 East Ave. L-223, Livermore, CA 94550

Tel: 925-423-1926, Fax: 925-422-2373, E-mail: hoel1@llnl.gov

\*also affiliated with Department of Applied Science, University of California at Davis

### Abstract

We present a novel micromachined sensor that couples a swellable hydrogel with capacitive detection. The hydrogel swells in response to analyte concentration, exerting contact pressure on a deformable conducting membrane. Results are presented for characterization of a PHEMA hydrogel swelling in response to a calcium nitrate solution. Pressure-deflection measurements are performed on NiTi-based membranes. Hydrogel-actuated deflections of the membranes are measured. These measurements are correlated to determine the pressure generating characteristics of the hydrogel. Membrane deflection techniques have not previously been employed for hydrogel characterization. The PHEMA sample exhibited greatest sensitivity in the pH range of 6.0 - 6.5 and performed an average of 2.8 Joules of work per  $\text{m}^3$  per pH unit in response to ambient conditions over the pH range 3.5 - 6.5. The membrane deflections correspond to capacitive shifts of about 4 pF per pH unit for a capacitive transducer with initial gap of 100  $\mu\text{m}$ , capacitor plate area of 18.5  $\text{mm}^2$ , and initial hydrogel volume of 11  $\mu\text{L}$ .

### Introduction

Hydrogels are a class of polymers with a high affinity for water, swelling as water is drawn into the polymer matrix. Ions in solution exert electrostatic forces on ionic polymer fibers. The balance of forces determines equilibrium inter-fiber distances. Longer distances admit greater volumes of fluid into the polymer complex, with the effect that hydrogels swell variably in response to solution characteristics, such as pH. Typical mass increases on hydration may be 10 to 100 times.

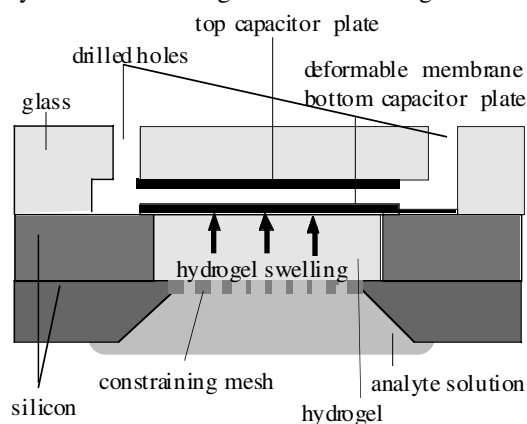
Hydrogels exhibit many characteristics that are useful in a biosensor material. They can be designed for sensitivity to specific pH ranges and salt concentrations, and to exhibit specific volume swelling ratios. Some are inert to normal biological processes, resistant to degeneration, not absorbed by the body, permeable to metabolites, permit water content similar to living tissue, withstand heat sterilization, and can be shaped [1]. In addition, hydrogels have been dissolved, applied, and patterned similarly to photoresist [2].

Hydrogel-based sensors have been utilized previously for measurement of pH and specific analytes, such as urea [3-4]. Analyte specificity has been achieved by embedding biomolecules in the hydrogel, which react with a specific analyte. The by-product of the reaction causes a pH change, so that the hydrogel response to the

pH change can be interpreted as a measure of analyte concentration. Previous MEMS applications have utilized the pH dependent conductance of hydrogels, measuring current as a function of concentration. Our application is distinct in that it utilizes the pH dependent swelling behavior to perform work. Although hydrogels have been used as structural materials in biotechnology, with applications such as contact lens material, electrophoresis gels, and prosthetics [5], they have not been commonly used as actuator materials. Capacitive detection techniques have often been used for pressure measurements in MEMS biosensing applications, for example blood pressure or intraocular pressure [6-9].

In this paper, we establish the viability of hydrogel swelling as an actuating mechanism in a capacitive detection system. Membrane deflections actuated by a known pressure source are compared with deflections actuated by a hydrogel swelling in response to a variable salt concentration. These measurements are used to assess the hydrogel's swelling force.

Hydrogel-Actuated Sensor The sensor is designed to passively convert changes in a biological analyte

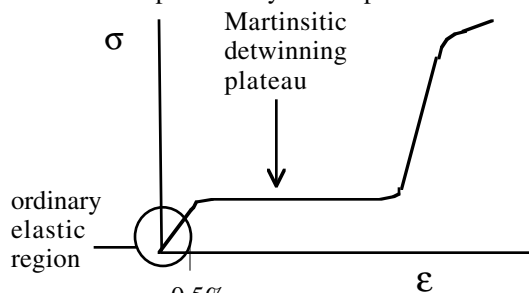


**Figure 1.** Diagram of hydrogel-actuated sensor. Hydrogel swelling in response to an analyte causes deflection of a conductive membrane and a resultant change in capacitance of a parallel plate capacitor.

concentration into an electromagnetic signal. Figure 1 shows a diagram of the design. The hydrogel is encapsulated within a silicon cell. One wall of the cell is a deformable conducting membrane. The opposite wall of the cell consists of a rigid silicon mesh etched with small holes. The mesh allows exposure of the hydrogel to the ambient analyte solution, while

constraining the hydrogel. A capacitor is completed by a second electrode in a glass etched cavity. The cavity depth determines the capacitor gap. Ultrasonically-drilled holes are used to make electrical contact through the glass, such that a surface mount inductor can be attached to form a resonant LC circuit. When the gel expands or contracts in response to variations in the analyte solution, the capacitor gap changes. A shift in resonance frequency results which can be probed remotely by a separate antenna circuit, producing a signal for analysis.

NiTi-based films were used for the deformable membrane because they are highly elastic and robust. Membrane deflection profiles were measured at pressures from 0 psi to 9.8 psi. The induced deflections resulted in strains below 0.2%. Shape-memory and superelastic behavior can also be achieved with these NiTi-based films. Those effects typically begin to be observed at about 0.5% strain, as shown in Figure 2 [10-12]. Although very large strains can be supported by shape memory behavior, heating is required for recovery of the unstrained film shape, which is unacceptable for our application. Little previous work has been done to characterize the material properties of NiTi films at small strains, due to greater interest in their shape memory and superelastic effects.



**Figure 2.** Stress versus strain for Martensitic shape memory alloy at room temperature.

## Methods

**Fabrication** For initial hydrogel characterization we designed structures with membrane areas from 3x3 mm<sup>2</sup> to 5x5 mm<sup>2</sup>. The membranes were formed by etching through the backside of a 500 μm thick {100} silicon wafer with 44% KOH:H<sub>2</sub>O solution. A 4000 Å low stress nitride film served as the masking layer. The NiTi film was DC magnetron sputter-deposited on the substrate following membrane formation. Ti was deposited first as an adhesion layer, then approximately 3.5 μm of NiTi-based alloy was deposited at 150 Watts power, at a substrate temperature of 575° C. The NiTi film was then lithographically patterned and etched in a solution of 20:20:1 HCl:HNO<sub>3</sub>:HF.

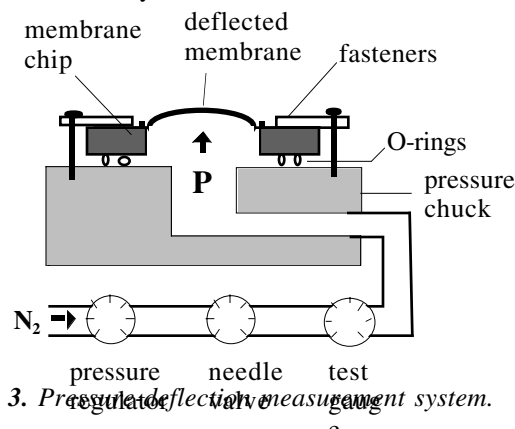
The mesh cavity was formed by partial etching of a silicon wafer from the backside with a 25% KOH:H<sub>2</sub>O solution, removing all but 100 μm silicon thickness. The front side was then patterned with a mesh pattern and etching was resumed from both sides, resulting in a 50 μm thick membrane with 100 μm holes. The membrane and mesh wafers were diced and the silicon cells were assembled.

To form cavities for the capacitor, 1.1 mm thick Pyrex wafers were photolithographically patterned using Au for

a masking layer, with a Cr adhesion layer. The cavities were etched using 1:4 HF:acetic acid. Cavity depth can be chosen to produce a specific operating range of capacitance. 1.0 mm holes were ultrasonically drilled, providing access for leads to connect a surface mount inductor with the capacitor. Films of Cr for adhesion and Au for conduction were sputtered into the cavities for electrodes and down one through-hole for a lead to connect the sputtered electrode with a surface mount inductor on the other side of the glass plate. A conducting polymer plug was inserted through the other hole to connect the inductor with the NiTi electrode.

**Hydrogel preparation** The hydrogel used in these measurements was Poly(2-hydroxyethyl methacrylate), (PHEMA). Preparation and assembly of the silicon cell were as follows. PHEMA crystals were dissolved in methanol and pipetted into the cavity of the mesh chip. The cavity bottom was lined with filter paper to prevent the gel from extruding through the holes under pressure. Optimal results (smooth surface and thoroughly dry) were achieved by using a thicker solution, 4:1 methanol:PHEMA by weight, for about 75% of the total PHEMA, which produced an irregular surface, then using a thin 8:1 solution for the last 25% to smooth it. Methanol was allowed to evaporate overnight. After drying, the PHEMA was rehydrated in DI water. For a 5x5 mm<sup>2</sup> cavity, 6.25 mg of dry PHEMA dissolved in 40 μL of methanol attained a volume of 11.2 μL when rehydrated in DI water. Mesh chips were bonded to membrane chips using Permabond 910.

**Testing** To characterize the stress-strain behavior and residual stress of the NiTi films, wafer curvature testing was performed on similarly deposited films using a Tencor FLX-2320 system.



**Figure 3.** Pressure deflection measurement system.

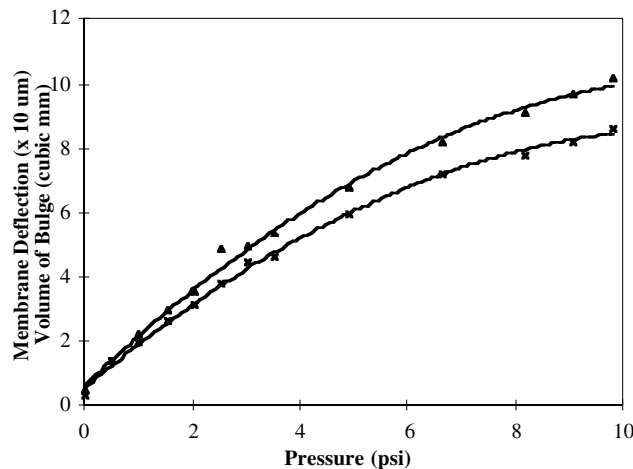
Prior to assembling the silicon cells, the NiTi membranes were characterized using a UBM scanning optical profilometer and the pressure chuck system, shown in Figure 3. Membrane deflections versus applied pressure were measured. The volume change of the bulged membrane was also measured on the profilometer. Hydrogel swelling was tested in ionic solutions of Ca(NO<sub>3</sub>)<sub>2</sub>•4H<sub>2</sub>O and DI water at concentrations of 0.5 M, 1.0 M, 1.5 M, 2.0 M, and 3.0 M. Chips were immersed in each solution for a minimum of two hours prior to testing to insure equilibration. To keep the PHEMA hydrated during measurement, the chips were mounted on a tray resting in a bath of solution. A hole in the tray provided a contact port. The tray also served to retard evaporation of the solution.

Measurements of deflection and volume change were made at each concentration. Results were compared with membrane pressure-deflection characteristics to determine pressure as a function of calcium nitrate concentration. The pH of ionic solutions was also measured to correlate pressure with pH.

## Results

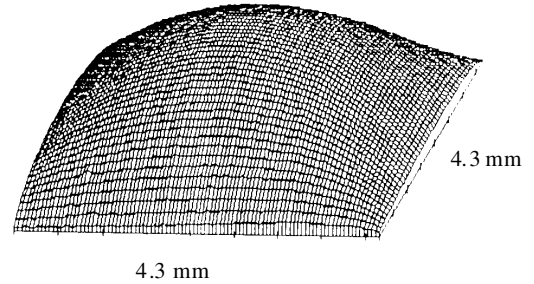
Wafer curvature testing verified that the NiTi films were slightly tensile at room temperature, as needed to avoid membrane buckling. Onset of shape memory behavior occurred at about 50°C. The films were fully Martensitic at room temperature, insuring that our testing would be outside of the shape memory regime. The strain at maximum deflection was 0.11%. Membrane strains induced in pressure tests were fully recovered on unloading.

Results for the membrane pressure measurements of a 18.5 mm<sup>2</sup> membrane are shown in Figure 4. The membrane response to air pressure was nearly linear up to about 3 psi, flattening gradually at higher pressures. The zero pressure surface profile was very slightly convex, probably due to stress in the substrate from the pressure chuck clamp. A least squares fit was calculated for extrapolating pressure values from the hydrogel deflection measurements.

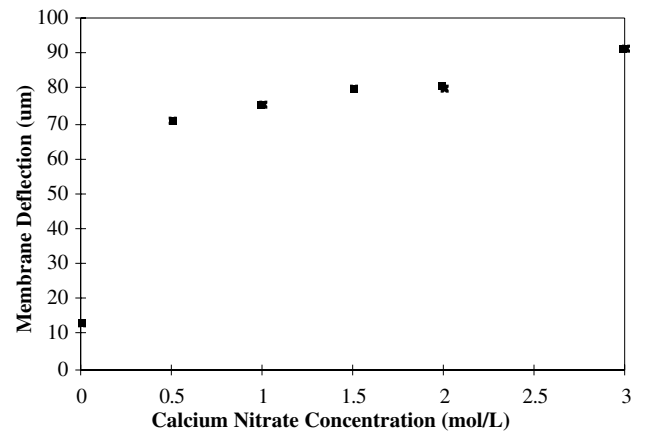


**Figure 4.** Optical measurements of NiTi membrane response to air pressure. Maximum deflection,  $\Delta$ . Volume of bulge, x.

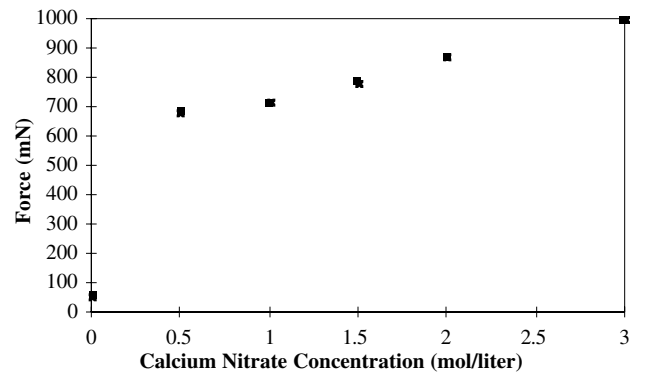
Deflections of the same membrane by hydrogel swelling were measured. Figure 5 shows an optically scanned profile of hydrogel-actuated swelling. Hydrogel chip measurements for maximum deflection versus calcium nitrate concentration are shown in Figure 6. The plot reveals that the hydrogel's greatest sensitivity was at concentrations below 0.5 M (between pH 6.0 and 6.5). At higher concentrations the response was nearly linear.



**Figure 5.** Surface profile of NiTi membrane deflected by hydrogel swelling. Maximum deflection is 76  $\mu$ m.



**Figure 6.** Maximum deflection of hydrogel-actuated membrane.



**Figure 7.** Force in milliNewtons = 127.8 \* Pressure in psi for a membrane of area 18.5 mm<sup>2</sup>.

These deflection measurements were correlated with the pressure-deflection characteristics of the NiTi membrane to calculate hydrogel swelling force as a function of salt concentration. Figure 7 shows this relation, with pressure expressed as force. Solution pH was also measured and correlated with pressure. Measured pH decreased linearly with concentration, with pH 6.0 at 0.5 M and pH 3.5 at 3.0 M.

## Discussion

The work done by the PHEMA hydrogel as a function of pH was calculated from the pressure-volume relation using

$$W = \int PdV. \quad (1)$$

Pressure as a function of volume was estimated by a quadratic least squares fit of the pressure versus volume measurements taken from the NiTi membrane. This function was integrated over the volume change measured between pH 6.5 and pH 3.5. The resulting estimate is 93 nJ of total work done by the hydrogel in changing from pH 6.5 to pH 3.5. This corresponds to 8.4 J per m<sup>3</sup> of hydrogel volume over the measured pH range, for an average of 2.8 J per m<sup>3</sup> of work per pH unit.

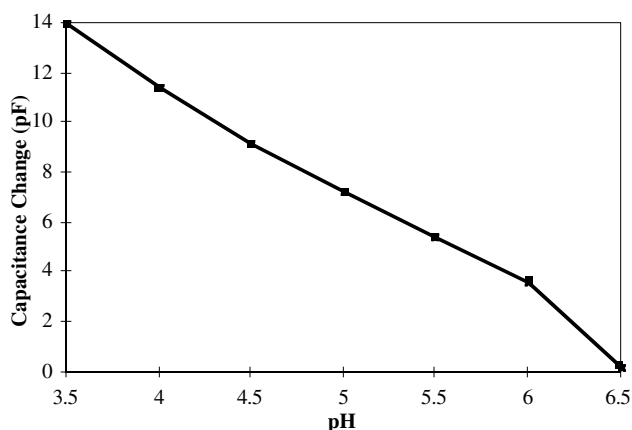
This appears to be a very small figure when compared with other microactuators, such as piezoelectric or electrostatic. However, this case is unique because the work is performed entirely from ambient conditions, with no external power source.

An estimate of the capacitance change as a function of pH and initial gap can be calculated by using the maximum deflection measurements to represent the final gap. The equation is

$$\Delta C = \epsilon_0 A(1/(G - D) - 1/G) \quad (2)$$

where A is the area of the capacitor plates, G is the initial gap, and D is the membrane deflection.

For the capacitance calculation, membrane deflection was represented as a function of pH by a logarithmic fit of the measured deflections. An initial gap of 100  $\mu$ m was assumed. As shown in Figure 8, the response was nearly linear, with changes in capacitance of about 4 pF per pH unit.



**Figure 8.** Estimated capacitance change over the measured pH range, assuming an initial gap of 100  $\mu$ m.

In summary, we have designed and fabricated a hydrogel-actuated sensor. Hydrogel swelling force was extrapolated from membrane deflection measurements. It was found that significant membrane deflections were achievable, demonstrating the viability of hydrogels as actuators for this type of capacitive sensor.

## References

- [1] J.D. Andrade [ed], *Hydrogels for Medical and Related Applications*, ACS Symposium Series, vol. 31, Washington, 1976.
- [2] Ph. Arquint, A. van den Berg, D.J. Strike, N.F. deRoos, and M. Koudelka-Hep, "Polymeric Membranes for Silicon Based (Bio)Sensors," *Journal of Biomaterials Applications*, vol. 7, July 1992, pp. 47-60.

- [3] N.F. Sheppard, Jr., R.C. Tucker, and S. Salehi-Had, "Design of a Conductimetric pH Microsensor Based on Reversibly Swelling Hydrogels," *Sensors and Actuators B*, vol. 10, 1993, pp. 73-77.
- [4] Th. Schalkhammer, Ch. Lobmaier, F. Pittner, A. Leitner, H. Brunner, and F.R. Aussenegg, "The Use of Metal-Island-Coated pH-Sensitive Swelling Polymers for Biosensor Applications," *Sensors and Actuators B*, vol. 24-25, 1995, pp.166-172.
- [5] J.D. Andrade [ed], *Hydrogels for Medical and Related Applications*, ACS Symposium Series, vol. 31, Washington, 1976.
- [6] G.T.A. Kovacs, *Micromachined Transducers Sourcebook*, WCB/McGraw-Hill, New York, NY, 1998.
- [7] L. Rosengren, P. Rangsten, Y. Backlund, B. Hok, B. Svedbergh, and G. Selen, "A System for Passive Implantable Pressure Sensors," in *Proc. 7th International Conference on Solid-State Sensors and Actuators*, June 1993, pp. 588-591.
- [8] B. Puers, A. van den Bossche, E. Peeters, and W. Sansen, "An Implantable Pressure Sensor for Use in Cardiology," *Sensors and Actuators A*, vol. 21-23, 1990, pp. 944-947.
- [9] H. Chau, and K.D. Wise, "An Ultraminiature Solid-State Pressure Sensor for a Cardiovascular Catheter," *IEEE Trans. Electronic Devices*, vol. 35, no. 12, December 1988, pp. 2355-2362.
- [10] T.W. Duerig, K.N. Melton, D. Stockel, C.M. Wayman, *Engineering Aspects of Shape Memory Alloys*, Butterworth-Heinemann Ltd., London, 1990.
- [11] P. Krulevitch, A.P. Lee, P.B. Ramsey, J.C. Trevino, J. Hamilton, and M.A. Northrup, "Thin Film Shape Memory Alloy Microactuators," *Journal of Microelectromechanical Systems*, vol. 5, no. 4, 1996, pp. 270-282.
- [12] K.P. Seward, P. Krulevitch, H.D. Ackler, and P.B. Ramsey, "A New Mechanical Characterization Method for Microactuators Applied to Shape Memory Films," in *International Conference on Solid State Sensors and Actuators, Transducers '99*, Sendai, Japan, 1999.

## Acknowledgments

Thanks to Conrad Yu for help with the pressure system, Phil Ramsey for sputtering the NiTi films, Julie Hamilton, Jim Trevino, Sony Lemoff, and Kirk Seward for processing advice, and June Yu and Jackie Crawford for materials. This work was conducted under the auspices of the Dept. of Energy by Lawrence Livermore National Laboratory, contract number W-7405-ENG-48.